Final Rejection dated July 3, 2002. Claims 1, 3-21, 23, and 25 have been cancelled. New claims 26-54 are submitted herein. Support for claims 26-54 can be found in the prior claims and throughout the application as filed. The number of claims has increased slightly in an attempt to clarify some of the issues raised by the Examiner under 35 U.S.C. § 112, as discussed in greater detail below. No new matter has been added. In view of the foregoing amendments and arguments that follow, Applicants respectfully request withdrawal of all rejections upon reconsideration.

Preliminarily, in response to Applicants' assertion in their previous response that prosecution has been protracted, the Examiner observed that there had been a reversal in position regarding the HS2 site as of the filing of the Declaration of Dr. Crombie April 6, 2001, thereby making new art available. Applicants respectfully submit that the prosecution history speaks for itself in this regard.

35 USC §112 rejections

Claims 1, 3-21, and 23 stand rejected under 35 USC §112 first paragraph. Claims 1, 3-21, and 23 have been cancelled. To the extent this rejection is applied to the newly added claims, Applicants argue the following.

The Examiner objects to the recitation of "A self-replicating origin of replication operative in mammalian host cells" allegedly on the grounds that "the specification does not provide support for the broader scope of replication origins that are operative in mammalian host cells" rather than just the viral origins of replication exemplified. (Final Rejection, page 3, emphasis in original.) The Examiner further stated that this is a new matter rejection. Applicants respectfully disagree that this recitation represents new matter. First, as was acknowledged by the Examiner, viral origins of replication are operative in mammalian host cells. Second, non-viral origins of replication operative in mammalian host cells are disclosed in the application as filed. On page 13, in paragraph 2, the application states the following.

> The self-replicating function may alternatively be provided by one or more **mammalian sequences** such as described by Wohlgemuth et al... , optionally in combination with one or more sequence which may be required for nuclear retention. The advantage of using mammalian, especially human sequences for providing the self-replicating function

> is that no extraneous activation factors are required which could have toxic or oncogenic properties. It will be understood by one of skill in the art that the invention is not limited to any one origin of replication or to any one episomal vector, but encompasses the combination of the tissue-restricted control of an LCR in an episomal vector.

(Emphasis added.)

Wohlgemuth et al. (copy is enclosed) describes the use of non-viral, mammalian sequences capable of providing a self-replicating function, which is clearly envisaged and disclosed in the application as filed. It is therefore respectfully suggested that the Examiner is incorrect in her assertion that "The specification does not contemplate or describe vectors comprising the particular genus of replication origins now recited in the claims (i.e., replication origins operative in mammalian host cells)." (Final Rejection, page 13.) However, the applicants apologise for any confusion caused by their not specifically pointing to this particular passage in the last response.

Claims 1, 3-21, 23, and 25 stand rejected under 35 USC §112, second paragraph as allegedly indefinite in the recitations of "episomal" and "for expressing a gene of interest extrachromosomally." Claims 1, 3-21, 23, and 25 have been cancelled. These recitations are not present in the newly submitted claims.

It is clear that there has been some confusion on both sides about the use, definition, and relevance of the terms "episome" and "episomal". The Examiner is quite correct that episomes are defined as having the ability to replicate both extrachromosomally and whilst chromosomally integrated. Applicants maintain that the definition of "episomal" is different. In this regard, Applicants note that the Woo et al reference appears to use the term "episomal" consistent with Applicants' use.

> The term "stable transformation" as used herein refers to episomal transformation in which the introduced therapeutic nucleic acid sequence or sequences is not incorporating into the chromosomes of the whole cell, but rather is replicated as an extra-chromosomal element.

(Woo *et al*, column 7, lines 18-22.) Nonetheless, to advance prosecution, Applicants have removed the recitation of "episomal" and added the recitation that the vector "replicates extrachromosomally" in the newly submitted claims.

Applicants also maintain that, "expression" is commonly used in two senses, applicable to both transcription and translation (as exemplified by title of the following: Connolly et al (2002), Plant Cell 14: 1347, "Expression of the IRT1 metal transporter is controlled by metals at the levels of transcript and protein accumulation", copy of abstract enclosed). Indeed, the Examiner herself uses the phrase "Expression of a gene, at the **protein** level..." apparently to distinguish the two uses (Final Rejection, page 5, emphasis added). In this latter sense, the Examiner is, of course, correct that this is always an extrachromosomal phenomenon. The present invention, however, concerns the novel and inventive provision of reliable tissue-specific *transcription* of a transgene on an extrachromosomal element. Examples 3 and 4 of the specification as filed, referring to Figures 4, 5 and 6, clearly assess expression in terms of the specific presence of **RNA** resulting from the transcription of the β-globin transgene. Nonetheless, to advance prosecution, the newly submitted claims recite "extrachromosomal transcription." Basis for this amendment can be found in Examples 3 and 4, as explained above.

Claims 1 and 6-11 stand rejected as allegedly indefinite in view of the recitation "for expressing a gene of interest in a host cell" because "the structural elements recited in the claims do not include a gene of interest." (Final Rejection, page 6.) Applicants respectfully disagree that the gene of interest must be included to make the claims definite. The claims are definite without this recitation.

> The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent.

MPEP § 2173. Nonetheless, Applicants have added a dependent claim (claim 37) reciting a gene of interest.

Claims 3-5 stand rejected as allegedly indefinite in their recitation of "wherein the component of an LCR is a component of the β-globin LCR." The Examiner's position was that it was unclear whether claims 3-5 were limited to a specific component because the claim from which claims 3-5 depended recited ". . .LCR, or component thereof." Applicants maintain that claims 3-5 are definite. Nonetheless, Applicants attempted to

clarify this point in the newly submitted claims by splitting out claims reciting components.

35 USC §102 rejections

Preliminarily, Applicants note with appreciation the withdrawal of the rejection of claims 1 and 2 over Safaya et al. Applicants disagree, however, with the assessment that the preamble was not to be accorded any weight.

> If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim.

MPEP 2111.02, citing *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999).

Claims 1 and 10 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Atweh *et al* (US Patent No. 6,022,738). Claims 1 and 10 have been cancelled. To the extent this rejection is applied to the newly submitted claims, Applicants submit the following arguments.

As addressed in Applicants' previous response, the vectors disclosed and claimed by Atweh *et al* only function when **integrated**. The vectors according to the Applicants' invention function when *not* integrated (i.e. when they are extrachromosomal). The Examiner argues that the vectors described by Atweh *et al* are plasmids and are, thus, extrachromosomal and, further, that they have all the structural elements recited in the Applicants' claims. The Examiner concludes, thus, that the functions are inherent. The Applicants respectfully submit that this is not so.

First, the Examiner's conclusion here that all plasmids are extrachromosomal seems contrary to her earlier statement that some plasmids integrate into the chromosome (see page 4 of the Final Rejection). Regardless, Atweh *et al* describes integrating plasmids.

Specifically, Atweh *et al* describes two types of vectors. The first is a bacterial phagemid constructed entirely for the purpose of manufacturing the retroviral vectors that are used for expression of the transgene of interest (see Column 12 "Example: Cloning of

N2A-γ Vector,). This vector is based on pBluescript II KS and thus contains a pUC **bacterial** plasmid origin of replication and an **f1 bacteriophage** origin of replication (See Column 12 lines 66-67 of Atweh *et al*, and the enclosed plasmid map). The phagemid does not, therefore, contain a "self-replicating origin of replication operative in **mammalian host cells**" as recited in the present claims. It should also be noted that no transcription of the transgene occurs in bacterial cells.

The second vector, termed N2A-γ, is derived from the first on transfection into producer mammalian cells. This is a replication-defective recombinant retrovirus capable of replication and packaging only in certain 'producer cell lines' (see Column 6, lines 23-45, Column 13 lines 10-19, of Atweh *et al*). As is the case for all retroviruses, replication follows *integration* and reverse transcription (see Column 13 lines 61-67, Figure 3 of Atweh *et al.* and Darnell *et al.*, *Molecular Cell Biology*, Scientific American Books, pp. 216-217, 1986, attached). It should be noted that, in these cells, there is no expression of the transgene, since the producer cells are not of the appropriate tissue type.

For expression, this virus is then allowed to transduce mammalian cells of a suitable tissue type (see Column 14, lines 30-39 of Atweh *et al*). Transcription, however, does not occur without integration. The viral vector contains long terminal repeats (LTRs) responsible for directing integration into the mammalian chromosome. The authors carefully establish the crucial integration required for success (Column 14, lines 38-39 of Atweh *et al*). This vector is capable of directing transcription in the permissive environment of the mammalian cell, but, being a replication-defective integrating retrovirus, it is not capable of "expressing a gene of interest extrachromosomally."

The Examiner refers to the column 4, lines 1-2 of Atweh *et al* where it is stated that "*Suitable vectors include viral and plasmid vectors known in the art.*" Column 3, lines 49-51, states that vectors provided relate to "*the transfer and expression of genes into erythroid cells*" and so the specification provides vectors suitable for this purpose. There is not the slightest hint, however, that such plasmids are capable of stable extrachromosomal maintenance and replication whilst providing tissue-specific, extrachromosomal transcription of a gene of interest. Even if there were doubt on any of these this points, MPEP 2112-51 states "*The fact that a certain result or characteristic*

may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." Indeed,

> [t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'

MPEP 2112, citing *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.

MPEP 2112, citing *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original) Since some plasmids function only when integrated, the Examiner cannot it does not necessarily flow that the extrachromosomal replication/transcription function is inherent in all plasmids. The Examiner has not met, nor can she meet, her burden for establishing inherency.

Regardless, the vectors of Atweh *et al* do not have "a self-replicating origin of replication operative in mammalian host cells" as recited by the present claims, nor can it be argued that such is inherent (see discussion above). The presence of a "self-replicating origin of replication operative in mammalian cells" represents a structural distinction over Atweh *et al.*

35 USC §103 rejections

Claims 6, 8, 9, 11, 12, 13, 17 and 19-21 stand rejected under 35USC §103 as allegedly obvious in light of Atweh *et al*, in combination with US Patent No. 5,674,703 (Woo *et al*). Claims 6, 8, 9, 11, 12, 13, 17 and 19-21 have been cancelled. To the extent this rejection is applied against the newly submitted claims, Applicants submit the following arguments.

The Examiner admits that Woo *et al* is cited simply as evidence that episomal

vectors having viral origins of replication were well known in the art at the time of filing of the instant application. (It is assumed that the Examiner is here recognizing that "episomal" means extrachromosomal.) As stated by the Applicants at several points in the past, this is not contested. What is contested is the motivation to combine the origins of replication and episomal vectors of Woo *et al* with LCRs.

Applicants respectfully suggest that the Examiner is misinterpreting the significance of the Atweh *et al* reference. Despite earlier arguing (correctly, the Applicants note) that the term "plasmid" includes *integrating* vectors, the Examiner here again insists that plasmids are extrachromosomal, citing column 4 lines 1-2 of Atweh *et al*. However, Atweh *et al*'s constructs do not function extrachromosomally. As discussed above, discussion incorporated herein, the particular vague and broad reference cited is to vectors suitable for the transfer and expression of genes into erythroid cells. It is not a reference to vectors suitable for extrachromosomal maintenance and replication whilst providing tissue-specific, extrachromosomal transcription of a gene of interest. No expression plasmids of this type are disclosed, discussed, or hinted at by the cited reference, which is concerned entirely with the construction and use of integrating retroviral vectors. The only LCR-containing plasmids disclosed in Atweh *et* al are for manufacturing the retroviral vectors and are not capable of being used as expression vectors directly.

The Examiner's central argument appears to be thus. Atweh *et al* discloses plasmid vectors comprising an LCR (this is uncontested). One of skill in the art would have immediately recognised that, for use in mammalian cells, such vectors would require suitable mammalian/viral origins of replication. Indeed, the Examiner also states (page 10, paragraph 3, of the Final Rejection) that such vectors in any case "already exist in the art". This is simply not true.

The problem addressed by the Applicants' invention is the provision of tissue-specific expression of a gene of interest by an expression vector that is stably maintained extrachromosomally in a mammalian cell. The expression (by which, as we have discussed, we mean *transcription*) occurs extrachromosomally from an expression vector that is being stably maintained (that is, is *replicating*) extrachromosomally in a

mammalian cell. Atweh *et al*'s vectors provide a means of *integrating* a transgene under the control of an erythroid-specific LCR, into the chromosome of a suitable erythroid cell. There was no motivation to introduce a viral origin of extrachromosomal replication for replication in mammalian cells because the Atweh *et al* vectors were already used in mammalian cells. Nor was there motivation to switch to a non-integrating vector. Indeed, if the intention of Atweh *et al* was simply to introduce a transgene under the control of a suitable LCR into erythroid cells, without integration, *why did they not do so?* It would have been considerably simpler to construct and manufacture such a vector than to manufacture replication deficient retrovirus in the way that they did. The reason is simple, and is explained by Dr. Antoniou (an expert in the field, working at the time) in his Declaration. The expectation would have been that **it would not have worked**. Indeed, in the absence of the Applicants' inventive contribution, extrachromosomal replication would have been regarded as *undesirable*.

On page 11of the Final Rejection, the Examiner appears to discount Dr. Antoniou's Declaration on the grounds that it addressed motivation when the compositions already existed in the art. Applicants maintain that the compositions as claimed did not exist in the art. The fact that the present rejection is based upon obviousness and not novelty contradicts the Examiner's assertion. Applicants request that the Examiner properly consider the Declaration. It is error not to do so. See *In re Beattie*, 974 F.2d 1309, 1313, 24 USPQ2d 1040, 1042-43 (Fed. Cir. 1992) (Office personnel should consider declarations from those skilled in the art praising the claimed invention and opining that the art teaches away from the invention.)

Claims 7, 9, 18 and 19 stand rejected for alleged obviousness in light of Atweh *et al* and Woo *et al*, additionally in light of Yates *et al.* Claims 7, 9, 18 and 19 have been cancelled. To the extent this rejection is applied against the newly submitted claims, Applicants argue the following.

Yates *et al* is cited as evidence that the use of the origin of replication of the Epstein-Barr virus to provide stable extrachromosomal replication of vectors in mammalian cells was well known in the art prior to the Applicant's filing date. This is, of course, not denied, as stated previously. However, the argument above regarding self-

replicating origins of replication operative in mammalian cells is equally applicable to the particular case of the EBV origin of replication as, probably, the best known of the suitable viral origins. The fact remains that there was no motivation to combine plasmid vectors comprising LCRs with *any* means of obtaining stable extrachromosomal maintenance in a mammalian cell.

It is earnestly requested that the Examiner reconsider the recitations in Applicants' claims, the actual detailed disclosures, and the Declaration of Dr Antoniou concerning the prevailing scientific prejudices at the time of filing, in assessing Applicants' claims.

Claim 23 stands rejected as allegedly obvious in light of Atweh *et al*, Woo *et al*, and, additionally, Chapman *et al*. Claim 23 has been cancelled. To the extent this rejection is maintained against any of the newly submitted claims, Applicants note that, as the Examiner states, Chapman is only cited to demonstrate common background art, which is uncontested. Chapman, therefore, does not overcome the deficiencies of Atweh *et al* and Woo *et al*.

Applicants respectfully submit that claims 26-53 are in condition for allowance. Applicants respectfully request early notification of the same. If the Examiner feels a telephonic interview would be helpful, she is asked to call the undersigned at 215-665-5593.

Attached hereto is a marked-up version of the changes made to the claims by the current Request for Reconsideration. The attached page is captioned "**Version With Markings to Show Changes**."

Respectfully submitted,

Date: October 3, 2002

Doreen Yatko Trujillo
Registration No. **35,719**

COZEN O'CONNOR
1900 Market Street, 6th Floor
Philadelphia, PA 19103-3508
(215) 665-2000 – Telephone
(215) 665-2013 – Facsimile

VERSION WITH MARKINGS TO SHOW CHANGES

In the claims:

Claims 1, 3-21, 23 and 25 have been canceled.

Claims 26-54 have been added.